Neuroimaging in predementia Alzheimer's disease

ten Kate, M.

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INTRODUCTION

ALZHEIMER'S DISEASE

Alzheimer's disease (AD) is a neurodegenerative disorder and the leading cause of dementia, with an estimated 36 million patients worldwide [1]. Patients typically present with progressive episodic memory loss, followed by decline in other cognitive functions, leading to interference with daily activities. The neuropathological hallmarks of AD are the accumulation of extraneuronal plaques, consisting of amyloid-beta proteins, and intraneuronal neurofibrillary tangles, consisting of hyperphosphorylated tau proteins [2]. These molecular changes are thought to result in cellular damage, impaired synaptic function and synaptic loss, and eventually neuronal death [3], which can be visualized as brain atrophy on magnetic resonance imaging (MRI). Cognitive impairment follows from this loss of synapses and neurons. The accumulation of amyloid plaques may start up to two decades before the onset of dementia [4,5]. The time period with progressive neuropathological changes in the absence of dementia is called the predementia stage of AD.

To date, there is no treatment available to cure AD or slow disease progression. Intervention in the predementia stage of the disease, when neuronal damage is still limited, could be an effective way of preventing cognitive decline. However, the development of therapeutic interventions in this early stage is hampered by an incomplete understanding of the predementia stage of AD. Major challenges are the diagnosis of AD before the onset of dementia and the identification of subjects at risk of imminent cognitive decline within the typical time frame of a clinical trial. This is complicated by the heterogeneous nature of AD, where patients differ in age of onset, genetic risk factors, and co-pathology such as cerebral small vessel disease, which might lead to different trajectories of disease.

In this thesis, we performed studies using structural MRI to characterize predementia brain changes in AD and to find predictors of cognitive decline and progression to dementia in non-demented subjects.

PREDEMENTIA STAGE OF ALZHEIMER'S DISEASE

The predementia stage of AD can be separated into preclinical AD (no cognitive impairment and evidence of AD pathology) and prodromal AD (mild cognitive impairment (MCI) and evidence of AD pathology) [6]. AD pathology can be detected *in vivo* with the use of biomarkers. Biomarkers are commonly divided into markers of amyloid pathology and markers of neuronal injury. Amyloid pathology can be assessed in cerebrospinal fluid (CSF), obtained by lumbar puncture, or on positron emission tomography (PET) scans using

amyloid-binding ligands. The presence of amyloid pathology is an important predictor of future cognitive decline in non-demented subjects [7,8]. However, amyloid pathology has limited prognostic value for the timing of dementia onset, as it reaches a plateau relatively early in the disease course [4,5,9]. Neuronal injury markers, such as brain atrophy measured on MRI, are more closely related to cognitive impairment and might therefore be useful for estimating time to clinical progression in non-demented subjects [10–13].

MRI IN ALZHEIMER'S DISEASE

Since the early nineties, brain MRI has been used to evaluate brain atrophy in patients presenting with dementia [14]. In patients with AD dementia, hippocampal atrophy is most typically observed (Figure 1), although considerable heterogeneity in atrophy patterns can be seen [15,16]. For example, patients with early onset AD dementia (≤ 65 years) may show more pronounced parietal atrophy [17]. Over the past years, there has been an increasing interest in using MRI to characterize brain changes in the preclinical and prodromal stages of AD. Identifying these brain changes is important, as they may serve as a biomarker for early diagnosis and prognosis in non-demented subjects.

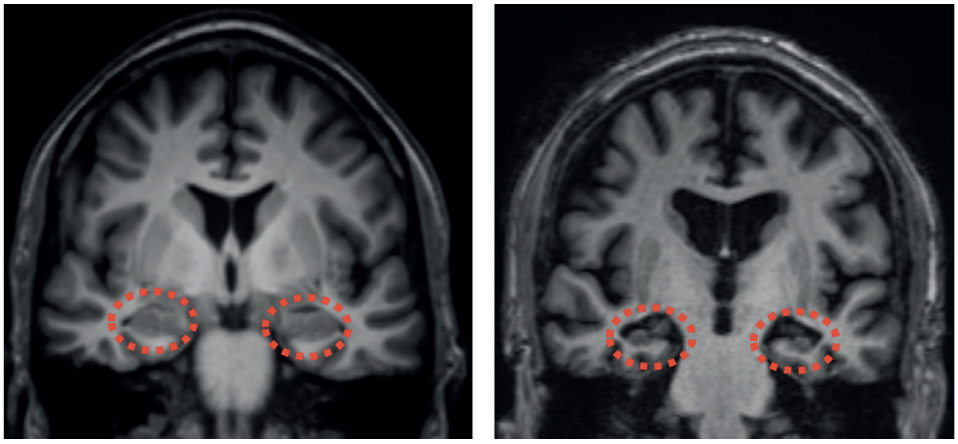

Figure 1: Structural brain MRI scans of a cognitively normal subject (left) and a subject with Alzheimer's disease dementia (right).

Displayed are coronal reconstructions of a 3D T1-weighted MRI scan. The MRI scan of the subject with AD dementia shows hippocampal atrophy (red circles).

In this thesis, we have primarily used structural T1-weighted MRI (Figure 1), which provides anatomical images of the brain on which grey matter tissue (and grey matter

atrophy) is clearly visualised. Various measures can be derived from structural MRI, which will be presented in the following paragraphs. We describe traditional methods as well as promising new technical developments in image analysis, which could inform on the predementia stage of AD.

Visual rating

A structural MRI scan can be visually assessed to detect gross atrophic changes (loss of brain tissue) associated with neurodegenerative diseases. Several dedicated visual rating scales have been developed to this end, which can easily be used in daily clinical practice [18]. In subjects with MCI, who suffer from cognitive impairment suggesting that a neurodegenerative process has already caused neuronal damage, gross atrophic changes can visually be detected with the use of these rating scales. In even earlier disease stages, atrophy may not be pronounced enough to be assessed by the naked eye. Advances in imaging analysis techniques permit the assessment of more subtle changes on structural MRI that precede gross atrophy.

Quantitative assessment

Volumetric measures of structures such as the hippocampus and entorhinal cortex can be reliably obtained from structural MRI using software that automatically segments these structures [19]. Another method to examine grey matter atrophy across subjects is voxel-based morphometry [20], which has the advantage that it avoids a priori selection of specific brain regions. The method involves segmenting the grey matter from structural MRI scans and spatially normalizing all individual segmentations into the same 3D space, allowing voxel-level statistical comparisons between subjects (Figure 2).

Subjects with MCI typically show hippocampal and cortical atrophy compared to cognitively normal subjects, but less atrophy than patients with AD dementia [21,22]. Within MCI, the presence of amyloid pathology has been associated with increased hippocampal atrophy [23,24]. In subjects with MCI and evidence of amyloid pathology (prodromal AD), it has been previously shown that hippocampal volume can predict time to progression to dementia [25,26]. It remains unknown whether other brain regions could further improve prediction of time to dementia in prodromal AD.

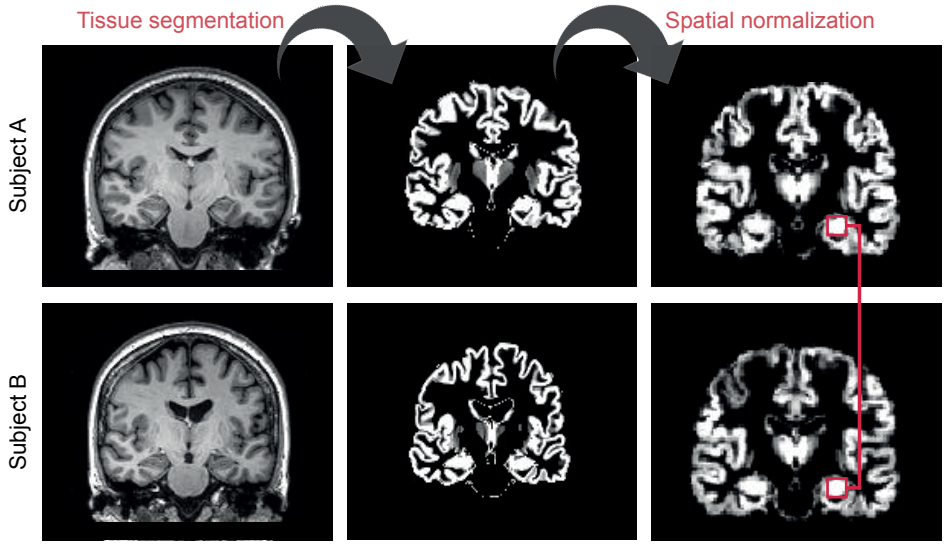

Figure 2: Principle of voxel-based morphometry.

First, grey matter tissue segmentations are extracted from individual structural MRI scans. Segmentations are then registered to a standardized space so that specific voxels represent the same anatomical structure across subjects (red cubes). Prior to statistical analysis, all segmentations are smoothed (not shown) to compensate for remaining anatomical differences between subjects.

Also in the preclinical stage of AD, structural brain changes might already be detectable. In cognitively normal subjects, low hippocampal volumes and decreased grey matter in temporal cortex, posterior cingulate and orbitofrontal regions have been associated with future progression to dementia [27–30]. However, it remains unclear when in the disease process the earliest structural brain changes can reliably be detected, and whether these could aid in prediction of time to clinical progression.

Grey matter network measures

Atrophic changes caused by neurodegenerative disease may not occur randomly, but rather follow changes in brain networks [31]. These changes in brain networks might therefore be detectable prior to atrophic changes. One way to measure brain networks is based on patterns of co-variation in grey matter structure across the brain, which can be represented as a network [32]. In cognitively normal subjects, brain networks tend to have a 'small-world' organization, which provides an optimal balance of specialized information processing and integration (Figure 3) [33,34]. In patients with AD dementia, grey matter network measures are disrupted, and seem to indicate a more random network organization [35–37]. It

remains unclear, however, when in the disease course of AD grey matter networks become abnormal and whether changes in grey matter networks could contribute to the prediction of cognitive decline.

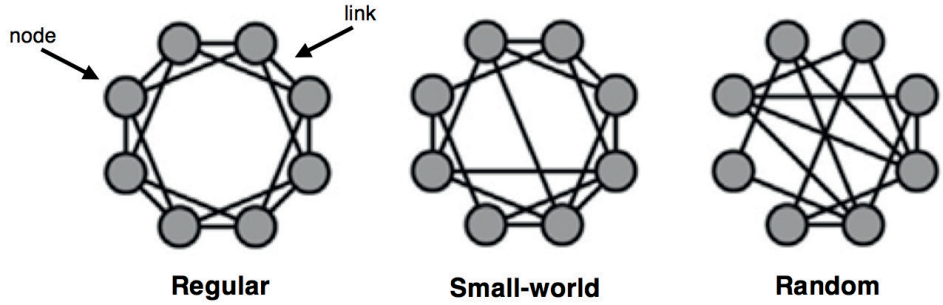

Figure 3: Examples of network organisation.

A network is composed of nodes (dots), which are connected by links (lines). The networks vary in complexity from completely regular to a random organisation. The regular network (left) is highly structured with all nodes connected to their immediate neighbours, but many steps needed to get from one side of the network to the other. The random network (right) has few steps between any two nodes in the network, but has no organisation. The small-world network (middle) is an intermediate, in which most nodes can be reached from another node by a small number of links, while still having local organisation. Brain networks in cognitively normal subjects tend to have a small-world organisation, which allows specialized (local) information processing by neighbouring nodes, while keeping short connections between distant areas.

Vascular pathology

MRI can also be used to detect vascular pathology (Figure 4) [38]. White matter hyperintensities (WMH) as seen on fluid-attenuated inversion recovery (FLAIR) scans are thought to reflect small-vessel disease in the brain. WMH may contribute to cognitive decline and could even be part of the pathological cascade of AD [39,40]. WMH are commonly found in elderly subjects, and have been associated with the occurrence of vascular risk factors. Twin studies have shown that both WMH and vascular risk factors are under strong genetic influence [41–45]. It is not yet clear whether there are common underlying genetic factors that influence both vascular risk factors and the presence of WMH.

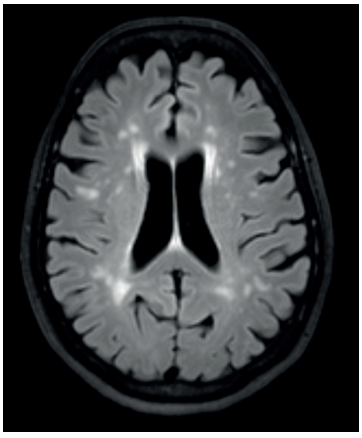

Figure 4: FLAIR scan showing white matter hyperintensities.

THESIS AIMS

In this thesis, we examined structural MRI measures in predementia AD. We defined predementia AD by the presence of amyloid pathology in either cognitively normal subjects (preclinical AD) or subjects with MCI (prodromal AD). Our goal was to obtain a better understanding of the pathological mechanisms underlying the development of AD, with the ultimate aim of improving diagnostic and prognostic markers in non-demented individuals. Using both traditional and novel imaging analysis techniques, we have examined structural and vascular brain changes in various large cohorts of non-demented subjects. We have specifically focussed on the following objectives:

1. Review the literature for neuroimaging markers for early diagnosis and prognosis in preclinical and prodromal AD;
2. Examine structural MRI changes in subjects at increased genetic risk for AD;
3. Examine MRI predictors of amyloid pathology in cognitively normal subjects and subjects with MCI;
4. Identify brain regions where grey matter atrophy is predictive of time to progression to dementia in prodromal AD;
5. Assess the potential of grey matter network measures as early diagnostic marker in preclinical AD;
6. Predict cognitive decline using grey matter networks in predementia AD;
7. Examine whether heterogeneity in atrophy patterns can already be detected in prodromal AD and can predict trajectories of cognitive decline;
8. Assess the genetic association between WMH and vascular risk factors in cognitively normal twins.

THESIS OUTLINE

In the first chapters of this thesis, we have reviewed the available literature on the use of neuroimaging measures during the predementia stage of AD. In **chapter 1** we review the use of neuroimaging markers to predict cognitive decline in predementia AD, and provide recommendations for the use of neuroimaging markers in clinical trials. In **chapter 2** we have examined the validity of hippocampal atrophy to be used in clinical practice to inform on progression to AD dementia in subjects with MCI.

In **chapter 3** we examined whether risk factors for amyloid aggregation and AD dementia, namely apolipoprotein E ε4 genotype and family history of dementia, are associated with grey matter atrophy in cognitively normal middle-aged adults.

In **chapter 4** we evaluate whether easily obtainable MRI measures are associated with amyloid pathology in non-demented subjects, and used machine-learning techniques to predict amyloid pathology.

In **chapter 5** we implemented voxel-level survival analysis to examine which brain regions can aid in the prediction of time to progression to dementia in subjects with prodromal AD.

In the following chapters, we have examined whether grey matter network measures can play a role in assessing and tracking early pathological changes in AD. In **chapter 6** and **chapter 7** we examined the association between grey matter network measures and amyloid pathology in cognitively normal subjects. We then evaluated whether grey matter network measures can aid in prediction of cognitive decline in subjects with preclinical and prodromal AD in **chapter 8**.

In **chapter 9** we performed a data-driven analysis of structural MRI data to find atrophy subtypes in patients with AD dementia. We then classified subjects with prodromal AD into these subtypes and examined whether atrophy subtype was predictive of the rate of clinical progression or decline in specific cognitive domains.

In **chapter 10** we examined the similarity of WMH in cognitively normal monozygotic twins to determine the upper limit of genetic contribution to this trait, as well as the relation between WMH and vascular risk factors.

We end this thesis by a summary and general discussion of the results from these studies.

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